**‘‘OUTLINE OF THE PROPOSED WORK FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN PHARMACEUTICAL SCIENCES’’**

**A SYNOPSIS**

# “Design, Synthesis and Biological Screening of Novel Pyrimidine Derivatives”

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Submitted

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# Ph.D. SYNOPSIS

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**Abstract:**

The chemistry of heterocyclic compounds is important for the discovery of novel drugs. Various natural compounds such as amino acids, alkaloids, vitamins, hormones, haemoglobin, and many synthetic drugs and dyes contain heterocyclic ring systems. Large numbers of synthetic heterocyclic compounds like pyrimidines, Pyrrole, Pyrrolidine, Furan, Thiophene, Piperidine, Pyridine and Thiazole show significant biological activity. Amongst these pyrimidine's are of great interest[1, 2]. After Scheele isolated uric acid in 1776, fused pyrimidine chemistry started. Pyrimidine is a six membered heterocyclic ring with two nitrogen (N) atoms in their ring. [It is a colourless compound, having molecular formula of C4H4N2 and molecular weight of 80 Dalton having melting point 22.5oC and boiling point 124$^{o}$C] Pyrimidine is a weaker base than pyridine, imidazole or amidines as addition of a proton does not increase the resonance energy like imidazole and amidines. The synthesis of pyrimidine derivatives have been an attracting extensive attention, as a wide range of such compounds played an important role in the field of medicinal chemistry as analgesic, anticonvulsant, anti-inflammatory, antimicrobial, anticancer activities etc.

Considering this fact in mind, it was felt worthwhile to select pyrimidine Moiety to design pyrimidine derivatives and evaluate synthesized derivatives for possible anti-mycobacterial, anticancer, and anticonvulsant activity.

## 1. Introduction:

Docking is a term used for computational schemes that attempt to find the "best" matching between two molecules: a receptor and a ligand. Molecular docking programs screen chemical databases for novel ligands that fit protein binding sites. When one compound fits the site well, close analogs typically do the same, so many of the compounds that are found in such screens resemble one another, thus reducing the variety and novelty of the compounds suggested.

Docking studies will be performed to gain insight into the most probable binding conformation of Pyrimidine derivatives for different biological activities and to compare derivatives which are in clinical use/trails. Docking studies will be performed by taking different molecules of reported synthesized Pyrimidine derivatives on different PDB crystal structures. [3]

In our present study molecular modeling studies like docking of reported Pyrimidine derivatives will be carried out. The data obtained from various docking tools like AUTO DOCK, GOLD, and Maestro from Schrodinger helps in comparing docking score of different Pyrimidine derivative. This study will help in understanding the molecular and structural basis of binding Pyrimidine's to different drug targets.

Docking is a method which predicts the preferred orientation of one molecule to another when bound to each other to form a stable complex. Molecular docking has become an increasingly important tool for drug discovery. Pharmacophore approaches have become one of the major tools in drug discovery after the past century's development. Various ligand-based and structure-based methods have been developed for improved pharmacophore modeling and have been successfully and extensively applied in virtual screening, *de novo* design and lead optimization. By considering these approaches, we are planning Docking and pharmacophore study for new pyrimidine derivatives for generating new Drug entity.

The main aim of these studies are for better understanding of drug resistance, function, receptor and drug flexibility, molecular mechanics of Pyrimidine and its derivative by molecular modeling . The data obtained in this study will help in understanding the multi-drug resistance and also the process of discovery of the antitubercular, anticancer drug and anticonvulsant drugs. It also helps in reducing the failure in drug development pipeline process yielding receptor specific drug candidates.

## 2. Literature Review:

1. G.m.v.n.a.r. Ravi Kumar et al reported 'Synthesis and Molecular Docking Studies of Novel 2-(2-Amino-6-Phenyl-4-Pyrimidinylamino) Ethanol Derivatives, Using Ring-Opening Reactions of Cyclic Ketene-*N*,*O*-Acetal', oriental journal of chemistry vol. 33, no. (3): pg.1555-1562[4]

2. Ahmed H Moustafa et al reported 'Design, Synthesis, Biological and Molecular Docking Studies of Some O-Hydroxycyanopyridine Derivatives' ,Pelagia Research Library Der ChemicaSinica, 2017, 8(3):313-332[5]

3. Mahmoud S. Bashandy et al reported 'Design, Synthesis and molecular docking of novel N,N-dimethylbenzenesulfonamide derivatives as potential antiproliferative agents',Journal of Enzyme Inhibition and Medicinal Chemistry29:5, 619-627, DOI:10.3109/14756366.2013.833197[6]

4. Sonia D. Arikkatt et al reported 'Synthesis and molecular docking studies of few novel Pyrimidine derivatives', Journal of Pharmacy Research 2014,8(2),93-97[7]

5. Zipeng Gong et al reported' Synthesis, Biological Evaluation and Molecular Docking Study of 2-Substituted-4,6-Diarylpyrimidines as Glucosidase Inhibitors' Molecules 2017, 22, 1865[8]

6. Zeinab A. Muhammad et al reported 'Synthesis, Antitumor Evaluation and Molecular Docking of New Morpholine Based Heterocycles' Molecules 2017, 22, 1211[9]

7. Hamada S Abulkhair1et al reported 'Molecular Docking, Synthesis and Biological Evaluation of Some Novel 2-Substituted-3-allyl-4(3H)-quinazolinone Derivatives as Anticonvulsant Agents', Med Chem (Los Angeles) 2016, 6:9[10]

**8.** Maryam Iman et al reported 'Docking, Synthesis and Anticonvulsant Activity of N-substituted Isoindoline-1,3-dione' ,Iranian Journal of Pharmaceutical Research (2017), 16 (2): 586-595[11]

**9.** Yasser K. Abdelmonem,et al reported 'Docking Studies, Synthesis, and Evaluation of Antioxidant Activities of N-Alkylated, 1,2,4-Triazole, 1,3,4-Oxa-, and Thiadiazole Containing the Aminopyrazolopyridine Derivatives', International Journal of Organic Chemistry, 2013, 3, 198-205[12]

**10.** Virupakshi Prabhakar et al reported 'Design, Synthesis, Characterization and Biological Activity of Novel Thieno[2,3-*d*]pyrimidine Derivatives' IJACS.2017.501005[13]

**11.** Rahaman S.K.A et al reported 'Synthesis and anti-histaminic activity of some novel pyrimidines' Saudi pharmaceutical journal 2009; 3; 17: 259-63.[14]

**12.** Shireesha B. et al reported 'Design, synthesis and antihistaminic activity of novel thieno [2, 3-d] pyrimidinones'International Journal of Pharmaceutical Sciences and Nanotechnology. 2008; 01; 02: 136-43.[15]

**13.** Xiang-lin Zhao et al reported 'Synthesis and anti-tumor activities of novel [1,2,4] triazolo [1,5-a] pyrimidines', Molecules 2007; 12: 1136-1146.[16]

**14.** Moni Sharma, Vinita Charturvedi, Manju Y.K, ShaliniBhatnagar and Prem M.S. Chauhan. et al reported 'Substituted quinolinylchalcones and quinolinylpyrimidines as a new class of Anti- infective agents', Eur J Med. Chem. 2009; 44: 2081-91.[17]

## 3. Aim and Objectives:

One-third of the world's population, almost 2 billion people, is infected, and the number of new TB cases each year climbed 6% between 1990 and 1997, from 7.5 million to 8 million cases, currently standing at 8.4 million. Epilepsy accounts for 0.6%, of the global burden of disease, a time-based measure that combines years of life lost due to premature mortality and time lived in less than full health and Cancer rates could further increase by 50% to 15 million new cases in the year 2020, according to the World Cancer Report. Nitrogen containing heterocyclic ring such as pyrimidine is a promising structural moiety for drug design. Pyrimidine derivatives form a component in a number of useful drugs and are associated with many biological and therapeutical activities Owing to the importance; we will design pyrimidine derivatives and evaluate synthesized derivatives for possible anti-mycobacterial anticancer, and anticonvulsant activity.

The present study aims to Design, synthesis and biological screening of novel pyrimidine Derivatives"

The present investigation would be carried out with following

**Objectives:**

1) To design Structural Library of pyrimidine derivatives.

2) Docking and pharmacophore study of pyrimidine derivatives.

3) To synthesize optimized derivatives of pyrimidine.

4) To characterize the synthesized compounds by different analytical techniques such as IR, $^{1}H$ ,$C^{13}$, NMR and mass spectral data, Elemental analysis.

5) To screen the synthesized compounds for their *in vitro*,Antitubercular,*anticancer* activities and anti-convulsion.

## 4. Methodology to be adopted:

### I. Sources of data

Databases like Chemical abstracts, Biological abstracts, Medline, and Journal of Chemistry section B, Indian Journal of Heterocyclic Chemistry, European Journal of Medicinal Chemistry, Bioorganic and Medicinal Chemistry Letters, Acta crystallographica, through Helinet etc.

### II. Method of collection of Data

**A.** Design of Structural Library by Substituting Different Groups on Pyrimidine Nucleus with Help of Chem draw, chem sketch.

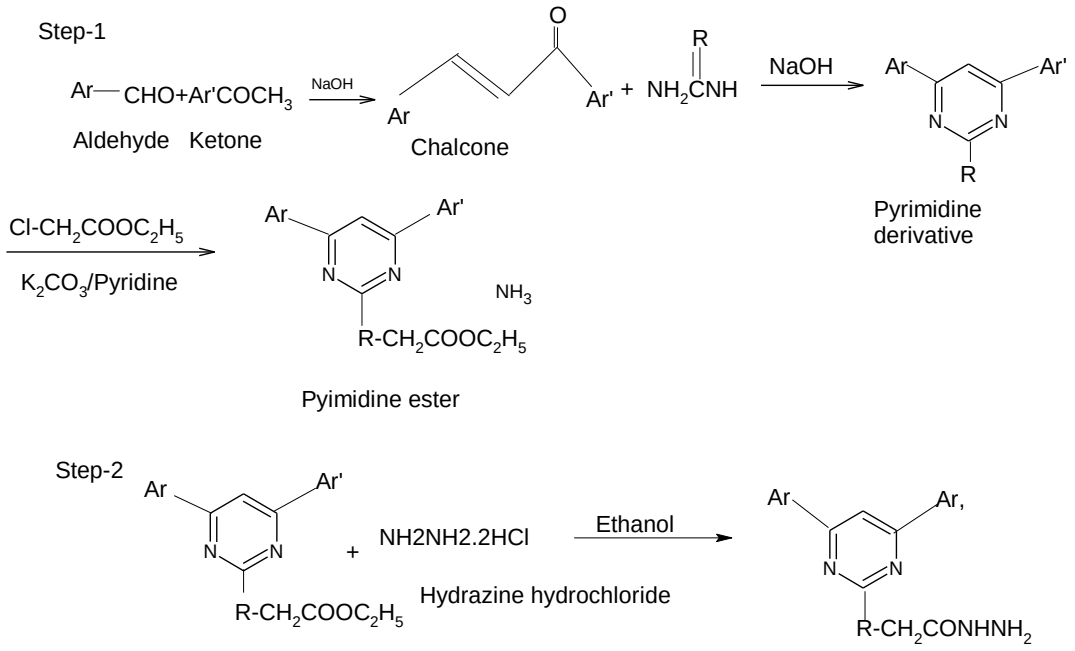
**B. Docking and pharmacophore study**

- **i.** Library structure of Pyrimidine derivatives will be docked in active site of enoylreductase (InhA), which in turn help to establish a structural basis of inhibition of mycobacteria.
- **ii.** Docking simulation will be performed to study interaction of telomerase (*3DU6*) to determine the probable binding model.
- **iii.** Docking simulation will be perform into the active site of GABA-A receptor
- **iv.** Pharmacophore Study on Pyrimidine Derivatives with respect to anti-tubercular, anticancer, and anticonvulsant.

**C. Synthesis of the Selected compounds:**

Chemicals and other reagents required for the synthesis will be procured from standard company sources. Compounds will be synthesized by using standard procedures. The reactions will be monitored by TLC and purification of the compounds will be carried out by recrystallization method using suitable solvent.

**D. Scheme for Synthesis:**




**E. Characterization of the compounds:**

The synthesized compounds will be characterized by preliminary laboratory techniques such as melting point, boiling point, TLC etc and by FTIR, $^{1}H$ NMR, C13analysis and mass spectroscopy, spectral data, and Elemental analysis.

**F. Biological Evaluation**

**a) Antitubercular**: Antitubercular activity will be evaluated against Mycobacteria.

**b) Anticancer activity**: The in *vitro* anticancer activity of Pyrimidine derivatives will be evaluated against different cell line**.**

**c) Anticonvulsant**: Anticonvulsant activity will be evaluated against Swiss albino mice.

## 5. Importance of study /society application:

Pyrimidine's are very important pharmacophores in medicinal chemistry, and exhibit a broad spectrum of biological activities, including antibacterial, antifungal, anti-inflammatory, antihypertensive, antiviral, anti-diabetic, anticonvulsant and anticancer activities. In addition to this, pyrimidine skeleton is also present in many natural products such as vitamin B1 (thiamine) and many clinically used drugs, such as trimethoprim, sulfadiazine, lamivudine, flucytosine. The present study aims to focus on account of important chemical moiety, that is, pyrimidine and its various derivatives. In the current studies we represent pyrimidines as with different mono-, di-, tri-, and tetra substituted classes which can facilitate the development of more potent and effective antimicrobial agents.

## 6. Proposed work plan:

| Sr.No. | Activity | Months |
|---|---|---|
| **1.** | Literature survey | **03** |
| **2.** | Docking and pharmacophore study | **06** |
| **3.** | Synthesis of optimized compound | **15** |
| **4.** | Biological Screening of synthesized compound | **06** |
| **5.** | Compilation, interpretation of data Thesis writing | **03** |
| **6.** | Submission of report | **03** |
| | **Total** | **36** |

## 7. References:


**1.** Delgado JN and Remers WA, Wilson and Giswold's- "Textbook of Organic Chemistry Medicinal and Pharmaceutical Chemistry," 10th ed. Philadelphia: Lippincott Raven, 1998.

**2.** Chala S. Dinakaran, " Fused pyrimidines: The heterocycle of diverse biological and pharmacological significance", Der Pharma Chemica, 2012, 4 (1), 255-265.

**3.** Hamada S Abulkhair1, "Molecular Docking, Synthesis and Biological Evaluation of Some Novel 2-Substituted-3-allyl-4(3H)-quinazolinone Derivatives as Anticonvulsant Agents Abulkhair et al., Med Chem (Los Angeles) 2016, 6:9.

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**21.** Naik TA, Chikhalia KH. "Studies on synthesis of pyrimidine derivatives and their pharmacological evaluation". E J chem 2007;4(1):60-6.